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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/502,698	02/11/2000	Shin-Ichi Funahashi	06501-056001	5541

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EXAMINER	
MERTZ, PREMA MARIA	
ART UNIT	**PAPER NUMBER**
1646	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/502,698	Applicant(s) Funahashi et al.
	Examiner Prema Mertz	Art Unit 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 19, 2002*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above, claim(s) *6-34* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5 and 35-37* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 6-34 are drawn to non-elected claims. Claim 2, amended claims 1, 3-5, and new claims 35-37 (Paper No. 13, 3/19/02), are under consideration.

2. Receipt of applicant's arguments and amendments filed in Paper No. 13 (3/19/02) is acknowledged.

3. The following previous rejections and objections are withdrawn in light of applicants amendments filed in Paper No. 6, 7/27/98:

(I) the rejection of claims 1-2, 4-5 under 35 U.S.C. § 112, second paragraph.

4. Applicant's arguments filed in Paper No. 13 (3/19/02), have been fully considered but were persuasive in part. The issues remaining are stated below.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 101

6. Claims 1-5, 35-37 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

This rejection is maintained for reasons of record set forth at pages 2-5 of the previous Office action (Paper No. 11, 9/11/01).

Applicants argue that Example 12 of the USPTO issued Utility Guidelines Training Materials entitled "Receptors", is particularly analogous to the instant situation. However, contrary to Applicants arguments, in the instant case, there is an asserted utility but no specific utility since it

applies to a whole class of proteins that bind to the PDZ-domain containing proteins of the instant invention. Furthermore, Applicants argue that the present specification (page 2, last to lines; page 3, lines 1-3) disclose that the proteins that bind to the PDZ-domain containing proteins of the instant invention, are involved in neural transmission, apoptosis and malignant conversion, they have recently drawn attention as targets for developing pharmaceuticals. The only disclosed function for a protein of the instant invention in the application as filed, however, is as a PDZ-domain containing proteins. It is certain that this protein can be employed to identify compounds which can act as agonist or antagonists, but this information is without real value because the instant specification does not identify a physiological process such as blood pressure, heart rate, taste, cognition, or sensation of pain which one could expect to influence by the administration of a compound that has been identified by employing a protein of the instant invention. If a protein of the instant invention was a receptor for a compound of any appreciable value then the protein would have utility in the purification of that compound, but the instant specification, as filed, does not identify any specific compound which is known to bind to the instantly claimed protein. Applicant is not being required to identify a ligand for the protein, **and** a physiological process mediated thereby **and** a disease or disorder for which that protein is a marker. Applicant is only required to identify **one** substantial, specific and credible utility and, as stated in the previous office action, the employment of this protein only as the subject of further research does not satisfy the utility requirement of 35 U.S.C. § 101 because the courts have interpreted this statute as requiring an invention to have "substantial utility" "where specific benefit exists in currently available form".

The instant proteins do not have a well-established utility because Applicants have not determined where the claimed proteins are expressed. For example, if it had been determined by Applicants that the instant proteins were only found in melanoma cell and binds to proteins that bind to the PDZ-domain containing proteins of the instant invention, then Applicants would have a well-established utility for the instantly claimed proteins. Therefore, all three prongs of the test have not been met and the utilities asserted for the present invention do not meet the credibility prong of the utility requirement as currently interpreted by the office.

An application has to be complete as filed, it is not a starting point of further research. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicants claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966)*, in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the Court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediate obvious or fully disclosed "real world" utility. The Court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit

exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion." The claimed protein are compounds which are known to be structurally analogous to proteins which have the PDZ domains and are known to bind to other proteins that have hydrophobic amino acid regions at their C-termini. In the absence of a knowledge of the natural ligands or biological significance of this protein in the instant specification as filed, there is no immediately obvious "patentable" use for it.

Each clinical agent which has been developed by measuring its interaction with a specific binding protein is evaluated against a receptor whose native ligand and physiological function are known, such as the adrenergic receptors, the dopamine receptors and the serotonin receptors There are also numerous G protein-coupled receptors, such as the odorant receptors, which do not mediate any clinically significant process. More importantly, an artisan knew, before they employed a specific receptor protein to identify clinically useful compounds, which physiological process or processes they wished to manipulate and that the receptor protein employed in their assay had an influence of that process. Even if one identifies an agonist or antagonist for a protein of the instant invention, this information is useless since one has no idea of what clinical effect the administration of that agonist or antagonist to an individual would have.

The following is an excerpt from M.P.E.P. 2138.05:

"CLAIMED INVENTION IS NOT ACTUALLY REDUCED TO PRACTICE UNLESS THERE IS A KNOWN UTILITY

Utility for the invention must be known at the time of the reduction to practice. Wiesner v. Weigert , 212 USPQ 721, 726 (CCPA 1981) (except for plant and design inventions); Azar v. Burns , 188 USPQ 601, 604 (Bd. Pat.

Inter. 1975) (a composition and a method cannot be actually reduced to practice unless the composition and the product produced by the method have a practical utility); Ciric v. Flanigen , 185 USPQ 103, 105 - 6 (CCPA 1975) ("when a count does not recite any particular utility, evidence establishing a substantial utility for any purpose is sufficient to prove a reduction to practice"; "the demonstrated similarity of ion exchange and adsorptive properties between the newly discovered zeolites and known crystalline zeolites ... have established utility for the zeolites of the count"); Engelhardt v. Judd , 151 USPQ 732, 735 (CCPA 1966) (When considering an actual reduction to practice as a bar to patentability for claims to compounds, it is sufficient to successfully demonstrate utility of the compounds in animals for somewhat different pharmaceutical purposes than those asserted in the specification for humans.); Rey - Bellet v. Engelhardt,181 USPQ 453, 455 (CCPA 1974) (Two categories of tests on laboratory animals have been considered adequate to show utility and reduction to practice: first, tests carried out to prove utility in humans where there is a satisfactory correlation between humans and animals, and second, tests carried out to prove utility for treating animals.).

A PROBABLE UTILITY MAY NOT BE SUFFICIENT TO ESTABLISH UTILITY

A probable utility does not establish a practical utility, which is established by actual testing or where the utility can be "foretold with certainty." Bindra v. Kelly , 206 USPQ 570, 575 (Bd. Pat. Inter. 1979) (Reduction to practice was not established for an intermediate useful in the preparation of a second intermediate with a known utility in the preparation of a pharmaceutical. The record established there was a high degree of probability of a successful preparation because one skilled in the art may have been motivated, in the sense of 35 U.S.C. 103, to prepare the second intermediate from the first inter mediate. However, a strong probability of utility is not sufficient to establish practical utility.); Wu v. Jucker , 167 USPQ 467, 472 (Bd. Pat. Inter. 1968) (screening test where there was an indication of possible utility is insufficient to establish practical utility). But see Nelson v. Bowler , 206 USPQ 881, 885 (CCPA 1980) (Relevant evidence is judged as a whole for its persuasiveness in linking observed properties to suggested uses. Reasonable correlation between the two is sufficient for an actual reduction to practice.)."

Therefore Applicants have failed to establish a practical utility for a protein of the instant invention at the time the application was filed.

Claims 1-5, 35-37 are also rejected under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to use the instant invention. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the

reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, first paragraph

7. Claims 1-2, 4-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for substantially pure polypeptides comprising the amino acid sequence as set forth in SEQ ID NO:1 or 2, does not reasonably provide enablement for substantially pure polypeptides comprising the amino acid sequence as set forth in SEQ ID NO:1 or 2, with upto 50 conservative substitutions or polypeptides comprising an amino acid sequence 85% or 90% identical to SEQ ID NO:1-2 or proteins encoded by a nucleic acid that hybridizes under high stringency conditions to a probe the sequence of which consists of SEQ ID NO:3, 59, 75, 78, 79, 80 or 81. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

This rejection is maintained for reasons of record set forth at pages 5-7 of the previous Office action (Paper No. 11, 9/11/01).

Applicants argue that the instant claims encompass both the wild-type proteins and "functional derivatives" thereof. The issue here is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. This position is consistent with the decisions in In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) and Amgen Inc. V. Chugai Pharmaceuticals Co. Ltd., 13 USPQ2d, 1737 (1990), and In re Wands, 8USPQ2d, 1400 (CAFC

1988) (which has been cited by Applicants. If Applicants will kindly review page 1404 of In re Wands, they will find that the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims. Applicants arguments that the standard is that of mutating a subject protein and testing to see if it retains the desired biological activity (in this case, maintains the affinity to the other proteins characteristic of the PDZ domain) is a position that has been routinely dismissed by the courts, as shown by the decisions cited above.

Further, In re Wands determined that the repetition of work which was disclosed in a patent application as producing a composition containing an antibody, which is a naturally-occurring compound, did not constitute undue experimentation even if the antibody produced thereby was not identical to those that were disclosed in that application. The instant claims are not limited to naturally-occurring compounds and the instant specification does not provide a description of a repeatable process of producing a protein whose amino acid sequence deviates from one of the two disclosed sequences by as much as 15%. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues of the two disclosed naturally-occurring sequences,

which are required for functional and structural integrity of those proteins. It is this additional characterization of the two disclosed proteins that is required in order to obtain the functional and structural data needed to permit one to produce a protein which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

Furthermore, Applicant is encouraged to review the discussion of 35 U.S.C. § 112, first paragraph, in a recent CAFC decision, Genentech, Inc. v. Novo. Nordisk, 42 USPQ2d, 100 (CAFC 1997), in which the decisions in In re Fisher, Amgen Inc. V. Chugai Pharmaceuticals Co. Ltd., and In re Wands were considered as the controlling precedents in determining enablement issues where protein and recombinant DNA issues are concerned. These decisions have been relied upon in the instant rejection and by the Court because they show that the judicial interpretation of the first paragraph of 35 U.S.C. § 112 requires that the breadth of claims must be based upon the predictability of the claimed subject matter and not on some standard of trial and error. To argue that one can make material embodiments of the invention and then test for those that work in the manner disclosed or that the instant claims only encompass the working embodiments is judicially unsound. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not, without actually making and testing them, then the instant application does not support the breadth of the claims. In the instant case it is highly improbable that any protein having 85% or 90% amino acid sequence identity to one of the two disclosed proteins will more likely than not perform

in the manner disclosed and the instant specification does not provide the guidance needed to predictably alter either of those two sequences with any reasonable expectation that the resulting protein will bind proteins that have a hydrophobic amino acid region at its C-terminus.

With respect to the rejection of claim 4, Applicants argue that the teachings of the present application, especially when taken together with the knowledge of one of ordinary skill in the pertinent art, provide an enabling disclosure for present claims 29 and 30. However, contrary to Applicants arguments, the cited portion of the specification (page 11, line 21 to page 12, line 2) merely outlines residues which are considered conservative. This is not adequate guidance as to the nature of the analogues or variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Therefore Applicants have not presented enablement commensurate in scope with the claims.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (703) 308-4229. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Prema Mertz

Prema Mertz Ph.D.
Primary Examiner
Art Unit 1646
May 20, 2002